REMARKS

This paper is submitted in response to the Office Action mailed July 16, 2003. Following this amendment, Claims 1, 4-20, 22-31, and 47-49 are pending. Claims 2 and 21 have been cancelled by this communication. Claims 1, 4, 5, 7, 8, 9, 10, 22, 23, 24, 27, 28, 47, 48, and 49 have been amended to more clearly indicate the subject matter which Applicants regard as the invention, and as discussed below. No new matter has been introduced by the amendment to the claims.

Claim Objections

The Examiner has objected to claim 10 under 37 C.F.R. 1.75 (c) as being in improper form for not referring to claims in the alternative. Claim 10 has been amended to correct the improper form.

Claims 21 and 22 have been objected to under 37 C.F.R. 1.75 (c) as being in improper form for failing to further limit the subject matter of a previous claim. Claim 21 has been cancelled. Claim 22 has been amended to depend from claim 14. As amended, the claim recites a specific plasmid as the DNA construct. Therefore, applicants submit that claim 22, as amended, further limits the subject matter of claim 14.

The Examiner has also objected to claim 47 under 37 C.F.R. 1.75 (c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. Claim 47 has been amended to correct the improper multiple dependencies.

Claims 7, 10, 23, 24, 27, 28, 48 and 49 are objected to for various informalities. These claims have been amended to correct the errors.

Therefore, Applicants respectfully request withdrawal of the objections to claims 7, 10, 22, 23, 24, 27, 28, 47, 48 and 49.

Rejections Under 35 U.S.C. § 112

The Examiner has rejected claims 1 and 3-6 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The Examiner states that the there is no evidence in the specification to support the limitation, "*cis*-acting nucleotide sequence does not comprise a full-length coding region." Claim 1 has been amended to delete this limitation.

The Examiner has also rejected claims 1, 3, 4-9, 11, 12-31, 48 and 49 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

The Examiner contends that these claims are readable on a genus of a *cis*-acting nucleotide sequence, which is capable of rendering the removal of introns from a precursor transcript encoded by a gene but not allegedly claimed in a specific biochemical or molecule structir that could be envisioned by one skilled in the art at the time of the invention. The Examiner states that the specification does not provide an adequate written description of a "genus" of *cis*-acting nucleotide sequence. The Examiner thus states that the disclosure provides sufficient support only for SEQ ID NO: 1 and 2, but not for the "generic" *cis*-acting nucleotide sequences of a representative number of species. The Examiner also states that the disclosure

provides sufficient support only for the *cis*-acting nucleotide sequences set forth in SEQ ID NOS: 1 and 2.

Applicants respectfully disagree. Applicants submit that the specification provides sufficient description of the claimed invention through the description of the functional characteristics, such as PKR-dependent splicing and sensitivity to 2-AP. The present invention is based on the discovery of a novel mechanism of regulating gene expression based on a *cis*-acting element that is specific to each gene. A "generic" *cis*-acting element is not defined in the specification using specific sequences, since such a basis for the element does not exist. The inventors have discovered that the *cis*-acting element is likely to be specific to the gene and may not share a common "structural" sequence with the *cis*-acting element of another gene. However, the Examiner has been unpersuaded by the arguments presented in the Amendment mailed May 5, 2003.

In the interest of furthering prosecution, applicants have amended claims 1 and 7 to recite the subject matter of the *cis*-acting element to consist essentially of the sequences of SEQ ID NOS: 1 and 2. The Examiner has indicated that the specification provides a sufficient description of SEQ ID NOS: 1 and 2. Therefore, these amendments should be sufficient in overcoming the written description rejection

With regard to claims 4, 5, 8 and 9, the Examiner has indicated that a nucleotide sequence whose complementary nucleotide sequence hybridizes with biologically functional fragments, derivatives, mutants and homologues of the nucleotide sequence as denoted by SEQ ID NOS: 1 and 2 would encompass a large number of nucleotide sequence and not meet the structural and/or functional limitations. The Examiner further alleges that it would take one

skilled in the art and undue amount of experimentation to make and/or use the complementary nucleotide sequences. Claims 4, 5, 8, and 9 have been amended to delete this subject matter.

Claims 21, 27, 48 and 49 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The insufficient antecedent basis of the limitations in these claims have been corrected by amendments to the claims.

For the foregoing reasons, Applicants respectfully request the withdrawal of the rejection of the claims.

Rejections Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-6 under 35 U.S.C. 102 (b) as being anticipated by Adams et al. (Genbank Accession No. T29839). The Examiner alleges that Adams discloses a nucleotide sequence with 99% identity to SEQ ID NO: 1 and 100% identity to SEQ ID NO:2. Applicants disagree.

Adams teaches the nucleotide sequence of a 248 base pair fragment of the human TNFα gene. Adams does not disclose a *cis* acting sequence which is capable of rendering the removal of introns from a precursor transcript, dependent upon activation of RNA-activated protein kinase (PKR) which is capable of phosphorylating the α-subunit of eukaryotic initiation factor 2 and consists essentially of the sequence set forth in SEQ ID NO:1, SEQ ID NO:2, or biologically functional fragments, derivatives, mutants and homologues thereof. The disclosure of the TNF-α fragments does not imply or even hint at the existence of a *cis*-acting element within the disclosed sequence. Such a disclosure also does not teach the skilled artisan of *cis*-

acting elements having unique splicing regulatory properties. Adams provides a mere disclosure of sequences from the TNFα gene, not the *cis*-acting sequence of the present invention.

In addition, Adams does not identify the specific nucleotide fragments 1069-1173 (SEQ ID NO:1) or 1073-1116 (SEQ ID NO:2) of the present invention. Therefore, the specific sequences are not afforded any significant feature or function, as claimed in the present invention.

Applicants also submit that the *cis*-acting sequences consist essentially of the sequences set forth in SEQ ID NO: 1 or 2 or biologically functional fragments, derivatives, mutants and homologues of the nucleotide sequence as denoted by SEQ ID NOS: 1 and 2. The use of such partically closed language in the claim clearly indicates to the skilled artisan that sequences from the TNFα gene other than the cis-acting sequences are excluded from the invention. The 248 base pair sequence taught by Adams includes sequences that are additional and unnecessary to the present invention. Adams clearly fails to teach the cis-acting sequences of the present invention. Therefore, Adams cannot anticipate the claims of the present invention.

The Examiner has rejected claims 7-9, 11, 13, 14, 21, 23, 24, 25, 27, 28, 29, 30, 31, 48 and 49 under 35 U.S.C. 102 (b) as being anticipated by Jarrous *et al.* ("Jarrous") The Examiner contends that Jarrous discloses a vector comprising the TNF-α gene including the 3' untranslated region, which reads on a *cis*-acting nucleotide sequence of the present application, a host cell transfected with the vector and further teaches that the trans-acting factor for the sequence is PKR.

Applicants respectfully disagree. Jarrous discloses a vector (phTNF-α) comprising the <u>full length</u> TNF-α gene, including the upstream regulatory sequences, a carrier

(salmon sperm DNA) and a host BHK-21 cell line transformed with said vector. The upstream regulatory sequences do not encompass the 3'-UTR. (See page 2815, first column, lines 17-18).

By contrast, the present invention provides for vectors comprising a defined *cis*-acting nucleotide sequence having specific properties of rendering the removal of introns from a precursor transcript, dependent upon activation of a *trans*-acting factor, which is an RNA-activated protein kinase capable of phosphorylating eIF2α, specifically, PKR and consisting essentially of the nucleotide sequence set forth in either SEQ ID NO:1, SEQ ID NO:2, or biologically functional fragments, derivatives, mutants and homologues thereof.

Jarrous makes no mention of the novel splicing control system disclosed by the present invention which involves the particular concomitant interaction of both a *cis*-acting element and a *trans*-acting element. Jarrous does not teach a trans-acting factor, such as PKR. Thus, Jarrous fails to teach that the splicing activity is dependent upon activation of a *trans*-acting factor, which is an RNA-activated protein kinase (PKR) capable of phosphorylating eIF2α.

Applicants further submit that the claims do not read on the vector as taught by Jarrous. Claim 7 has been amended to include a limitation wherein the *cis*-acting nucleotide sequence consists essentially of a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, and biologically functional fragments, derivatives, mutants and homologues thereof, thereby excluding the full TNFα gene. In contrast, the vector taught by Jarrous must include the full-length TNFα gene, and the untranslated region, but not essentially the specific sequence as set forth in SEQ ID NO:1 or SEQ ID NO:2.

Furthermore, the present invention demonstrates that a fragment of 104 base pairs in the well over 3,000 base pair sequence of the TNFα gene activates PKR at the RNA level and that this short fragment when inserted into the TNFα gene renders splicing of that gene dependent upon the activation of PKR. There is no disclosure or guidance in Jarrous to provide one of skill in the art of the mechanism exhibited by the vector of claim 7. Therefore, Jarrous cannot anticipate claims 7-9, 11, 13, 14, 21, 23, 24, 25, 27, 28, 29, 30, 31, 48 and 49 of the present invention.

For the foregoing reasons, Applicants respectfully request withdrawal of the rejection of claims 1-6, 7-9, 11, 13, 14, 21, 23, 24, 25, 27, 28, 29, 30, 31, 48 and 49 under 35 U.S.C. 102 (b).

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests withdrawal of the outstanding rejections and allowance of the pending claims.

Applicants have enclosed the fee for a three-month extension of time as required under 37 C.F.R. §1.17(a)(3). Applicants do not believe that any additional fee is required for this filing. Nevertheless, the Commissioner is hereby authorized to charge any fees required for this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Two copies of this page are enclosed.

Respectfully submitted,

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